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EXAMINER	
FORMAN, BETTY J	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/882,193	EMPEDOCLES ET AL.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 23-26* is/are pending in the application.

4a) Of the above claim(s) *27-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). *0403*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 11 August 2003 and 19 November 2003 in which claims 1, 17 and 18 were amended and claims 20-22 were canceled. All of the amendments have been thoroughly reviewed and entered. The previous rejections under 35 U.S.C. 102 and under 13 U.S.C. 103 in the Office Action dated 10 February 2003 are withdrawn in view of the amendments. The previous rejection under obviousness-type double patenting is maintained. All of the arguments have been thoroughly reviewed but are deemed moot in view of the amendments, withdrawn rejections and new grounds for rejection. New grounds for rejection necessitated by amendment are discussed.

Claims 1-19 and 23-26 are under prosecution.

Election/Restrictions

2. Applicant's traversal of the previous restriction requirement is acknowledged. The traversal is on the grounds that it would not be undue burden to examine the newly added claims along with the previously presented claims. However, it is maintained that undue burden would be required to examine the newly added claims along with those examined as evidenced by the fact that the new and previously examined claims have acquired a separate status in the art as recognized by their divergent subject matter and because a search of the subject matter of previously examined claims would not be co-extensive with a search of newly added claims. Specifically, the subject matter of the examined claims encompasses detecting quantum dots attached to target molecules and resolving optical characteristics of the

quantum dots to count the molecules. In contrast, the subject matter of added claims encompasses mutant DNA, wild-type DNA, sequence-tagged probes and hybridizations none of which is encompassed by the subject matter of the examined claims.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-3, 17, 19 and 23-26 rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss et al (U.S. Patent No. 6,207,392 B1, filed 1 March 1999) in view of Barbera-Guillem et al (U.S. Patent No. 6,221,602, filed 9 November 1999).

Regarding Claim 1, Weiss et al disclose a method of detecting the presence of at least one target nucleic acid sequence (i.e. detectable substance, Column 4, lines 15-20, 28-35 and 54-56) in a sample comprising: detecting the optical characteristic of a first and second quantum dot attached to a target nucleic acid sequence (Column 12, lines 7-37); and detecting the labeled target nucleic acid by detecting fluorescence emitted by the quantum dot wherein detection of fluorescence in the sample indicates the presence of at least one target nucleic acid

sequence, wherein the labeling is via bonding of the nucleic acid affinity molecule to its complementary sequence (Column 4, lines 27-47 and Claim 114).

Weiss et al do not specifically teach resolving the quantum dot to count the single molecule. However, Barbera-Guillem et al teach a similar method wherein quantum dots are resolved to count individual molecules whereby nucleobases incorporated into the molecules are analyzed for sequencing (Column 18, lines 4-54). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the resolving of Barbera-Guillem et al to the method of Weiss et al to thereby resolve individual quantum dots for the expected benefit of sequencing the molecule based on the resolution as taught by Barbera-Guillem et al (Column 18, lines 4-54).

Regarding Claim 2, Weiss et al disclose the method further comprising quantitating the target sequence by analyzing the detected emitted fluorescence (Column 19, lines 41-48 and Claim 127).

Regarding Claim 3, Weiss et al disclose the method further comprising transcribing the target nucleic acid sequence i.e. PCR (Column 25,line 62-Column 26, line 48).

Regarding Claim 17, Weiss et al disclose a method of detecting the presence of at least one target nucleic acid sequence in a sample (i.e. detectable substance) in a sample comprising: labeling at least one target nucleic acid sequence with at least one quantum dot; and detecting the labeled target nucleic acid by detecting fluorescence emitted by the quantum dot wherein detection of fluorescence in the sample indicates the presence of at least one target nucleic acid sequence; and quantitating the target sequence by analyzing the detected emitted fluorescence, wherein the labeling is via bonding of the nucleic acid affinity molecule to its complementary sequence (Column 4, lines 27-47 , Column 19, lines 41-48 and Claims 114 and 127).

Regarding Claim 19, Weiss et al disclose teach the method wherein said optical characteristic of the quantum dot is detected by coincidence detection (Column 17, lines 11-31).

Regarding Claim 23, Weiss et al disclose the method wherein the quantum dots are distinguishable by an optical characteristic selected from fluorescence spectrum, fluorescence emission, fluorescence excitation, uv absorbance visible light absorbance, fluorescence quantum yields fluorescence lifetime and light scattering (Column 18, line 57-Column 19, line 33).

Regarding Claim 24, Weiss et al disclose the method wherein the optical characteristic is fluorescence (Column 18, line 57-Column 19, line 16).

Regarding Claim 25, Weiss et al disclose the method wherein the first and second dots are distinguishable as a first and second color (Column 17, lines 11-31).

Regarding Claim 26, Weiss et al disclose the method wherein the first and second color combine to form a third color that is distinguishable (Column 17, lines 11-31).

5. Claims 1-8, 17-19, 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singer et al (U.S. Patent No. 5,866,331, issued 2 February 1999) in view of Bawandi et al (U.S. Patent No. 6,306,610, filed 17 September 1999) and Barbera-Guillem et al (U.S. Patent No. 6,221,602, filed 9 November 1999).

Regarding Claim 1, Singer et al teach a method of detecting the presence of a single copy of a target nucleic acid in a sample the method comprising detecting an optical characteristic of a first and second label attached to said single copy wherein said first and second label are distinguishable thereby detecting said single copy of the target nucleic acid (Abstract, Column 1, lines 45-67 and Claim 1) but they do not teach the label is a quantum

dot. However, quantum dot labels were well known in the art at the time the claimed invention was made as taught by Bawandi et al. Bawandi et al teach a similar method comprising detecting an optical characteristic of quantum dots attached to a target wherein quantum dots are distinguishable (Column 27, lines 23-36 and Example 10, Column 34, lines 29-55) and they also teach the advantages of quantum dots i.e. broad range of excitation wavelengths, high fluorescent intensity, target affinity, facilitate detection of location and binding of target, emission spectra of line widths as narrow and 25-30 nm, high resolution linewidths all of which facilitate simultaneous detection and discrimination of a plurality of targets (Column 4, lines 7-56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labels of Singer et al with the quantum dot labels of Bawandi et al based on the quantum dot advantages taught by the later i.e. broad range of excitation wavelengths, high fluorescent intensity, target affinity, facilitate detection of location and binding of target, emission spectra of line widths as narrow and 25-30 nm, high resolution linewidths all of which facilitate simultaneous detection and discrimination of a plurality of targets (Column 4, lines 7-56).

Bawandi et al teach the method further comprising resolving the optical characteristic of the first and second quantum dot from an optical characteristic not attached to the single copy (Column 21, lines 10-31).

Bawandi et al and Singer et al do not specifically teach resolving the quantum dot to count the single molecule. However, Barbera-Guillem et al teach a similar method wherein quantum dots are resolved to count individual molecules whereby nucleobases incorporated into the molecules are analyzed for sequencing (Column 18, lines 4-54). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the resolving of Barbera-Guillem et al to the method of Bawandi et al and Singer et al to thereby resolve individual quantum dots for the expected benefit of sequencing the molecule based on the resolution as taught by Barbera-Guillem et al (Column 18, lines 4-54).

Regarding Claim 2, Singer et al teach the method further comprising quantitating the target by analyzing the detected optical characteristics (Column 7, lines 13-18).

Regarding Claim 3, Singer et al teach the method further comprising transcribing the target nucleic acid i.e. mRNA is produced by the cell prior to in situ hybridization (Column 11, line 56-Column 12, line 4).

Regarding Claims 4, 5 & 7, Singer et al teach the method wherein the target is transcribed (Column 11, line 56-Column 12, line 4) but they do not teach the target comprises DNA transcribed using a primer which anneals to a conserved region of the DNA and transcribes a polymorphic region. However, Bawandi et al teach the similar method wherein the target is transcribed DNA comprising a polymorphic region (Column 20, lines 11-27) and provides a biotinylated DNA and the substrate is comprises streptavidin (Example 10, Column 34, lines 29-55). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the polymorphic DNA target of Bawandi et al to the nucleic acid target of Singer et al based on the polymorphic interests and preference taught by Bawandi et al (Column 20, lines 24-27) for the expected benefit of detecting diagnostically important nucleic acids.

Regarding Claim 6, Singer et al teach the method further comprising binding the transcribed target to a substrate (Column 11, line 62-Column 12, line 52).

Regarding Claim 8, Singer et al disclose the method further comprising removing unbound portions of the target (Column 12, lines 27-33).

Regarding Claim 17, Singer et al teach a method of detecting the presence of a single copy of a target nucleic acid in a sample comprising detecting an optical characteristic of a first and second label attached to said single copy wherein said labels are distinguishable thereby detecting a single copy of said target and quantitating the target by analyzing the detected emitted fluorescence (Abstract, Column 1, lines 45-67 and Claim 1) but they do not teach the label is a quantum dot. However, quantum dot labels were well known in the art at the time

the claimed invention was made as taught by Bawandi et al. Bawandi et al teach a similar method comprising detecting an optical characteristic of quantum dots attached to a target wherein quantum dots are distinguishable (Column 27, lines 23-36 and Example 10, Column 34, lines 29-55) and they also teach the advantages of quantum dots i.e. broad range of excitation wavelengths, high fluorescent intensity, target affinity, facilitate detection of location and binding of target, emission spectra of line widths as narrow and 25-30 nm, high resolution linewidths all of which facilitate simultaneous detection and discrimination of a plurality of targets (Column 4, lines 7-56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labels of Singer et al with the quantum dot labels of Bawandi et al based on the quantum dot advantages taught by the later i.e. broad range of excitation wavelengths, high fluorescent intensity, target affinity, facilitate detection of location and binding of target, emission spectra of line widths as narrow and 25-30 nm, high resolution linewidths all of which facilitate simultaneous detection and discrimination of a plurality of targets (Column 4, lines 7-56).

Regarding Claim 18, Singer et al disclose a method of detecting the presence of a single copy of a target comprising transcribing said single copy immobilizing said target on a solid support, contacting the immobilized target with a hybridization probe, detecting an optical characteristic of the label and probe to thereby detect the single copy (Abstract, Column 1, lines 45-67 and Claim 1) but they do not teach the label is a quantum dot and they do not teach using a primer comprising an immobilizable label to form an immobilizable target. However, quantum dot and immobilizable labels were well known in the art at the time the claimed invention was made as taught by Bawandi et al. Bawandi et al teach a similar method comprising detecting an optical characteristic of quantum dots attached to a target wherein quantum dots are distinguishable and wherein the DNA is transcribed to provide an immobilizable target (Column 27, lines 23-36 and Example 10, Column 34, lines 29-55) and they also teach the advantages of quantum dots i.e. broad range of excitation wavelengths,

high fluorescent intensity, target affinity, facilitate detection of location and binding of target, emission spectra of line widths as narrow and 25-30 nm, high resolution linewidths all of which facilitate simultaneous detection and discrimination of a plurality of targets (Column 4, lines 7-56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labels of Singer et al with the quantum dot labels of Bawandi et al based on the quantum dot advantages taught by the later i.e. broad range of excitation wavelengths, high fluorescent intensity, target affinity, facilitate detection of location and binding of target, emission spectra of line widths as narrow and 25-30 nm, high resolution linewidths all of which facilitate simultaneous detection and discrimination of a plurality of targets (Column 4, lines 7-56).

Regarding Claim 19, Bawandi et al teach the method wherein said optical characteristic of the quantum dot is detected by coincidence detection (Column 27, lines26-30).

Regarding Claim 23, Bawandi et al teach the method wherein the quantum dots are distinguishable by an optical characteristic selected from fluorescence spectrum, fluorescence emission, fluorescence excitation, uv absorbance visible light absorbance, fluorescence quantum yields fluorescence lifetime and light scattering (Column 15, lines 9-49).

Regarding Claim 24, Bawandi et al teach the method wherein the optical characteristic is fluorescence (Column 15, lines 9-49).

Regarding Claim 25, Bawandi et al teach the method wherein the first and second dots are distinguishable as a first and second color (Column 14, lines 38-62).

Regarding Claim 26, Bawandi et al teach the method wherein the first and second color combine to form a third color that is distinguishable (Column 14, lines 38-62).

6. Claims 4-15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss et al (U.S. Patent No. 6,207,392, filed 1 March 1999) and Babera-Guillem et al (U.S. Patent No. 6,221,602, filed 9 November 1999) as applied to Claim 1 above and further in view of and Söderlund et al (U.S. Patent No. 6,013,431, filed 2 December 1993) in view of Chan et al (Science, 25 September 1998, 281: 2016-2018).

Regarding Claim 4, Weiss et al teach a method of detecting the presence of a single copy of target nucleic acid sequence (i.e. detectable substance, Column 4, lines 15-20, 28-35 and 54-56) in a sample comprising: detecting the optical characteristic of a first and second quantum dot attached to a target nucleic acid sequence (Column 12, lines 7-37); and detecting the labeled target nucleic acid by detecting fluorescence emitted by the quantum dot wherein detection of fluorescence in the sample indicates the presence of at least one target nucleic acid sequence, wherein the labeling is via bonding of the nucleic acid affinity molecule to its complementary sequence (Column 4, lines 27-47 and Claim 114) and further comprising transcribing the target nucleic acid sequence i.e. PCR (Column 25,line 62-Column 26, line 48).

Weiss et al do not specifically teach resolving the quantum dot to count the single molecule. However, Barbera-Guillem et al teach a similar method wherein quantum dots are resolved to count individual molecules whereby nucleobases incorporated into the molecules are analyzed for sequencing (Column 18, lines 4-54). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the resolving of Barbera-Guillem et al to the method of Weiss et al to thereby resolve individual quantum dots for the expected benefit of sequencing the molecule based on the resolution as taught by Barbera-Guillem et al (Column 18, lines 4-54).

Weiss et al do not specifically teach the transcribing provides a polymorphic region of DNA. However, transcribing a target sequence via PCR to produce polymorphic regions of DNA was well known and routinely practiced in the art at the time the claimed invention was made as taught by Söderlund et al. who teach a similar method of target detection comprising:

labeling at least one target nucleic acid sequence; and detecting the labeled target nucleic acid and they specifically teach transcribing the target using a primer which anneals to a conserved region of DNA to transcribe a polymorphic region of DNA (Example 1, Column 9, line 50-Column 11, line 52). Additionally, Söderlund et al teach that because numerous inherited diseases are caused by polymorphisms, methods for detecting polymorphic regions is are clinically important (Column 1, lines 35-65). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the transcription of a polymorphic target region of Söderlund et al to the transcription of Weiss et al based on the clinical importance of polymorphisms as taught by Söderlund et al (Column 1, lines 35-65). Therefore, one skilled in the art would have been motivated to transcribe and detect polymorphic regions of DNA for the obvious benefits of diagnosing clinically important DNA sequences.

Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the radioactive label and detection of Söderlund et al with the quantum dot labeling and detecting as taught by Weiss et al because it was well known in the art that radioactive labels are hazardous and short lived as taught by Chan et al (first paragraph). Chan et al also teach that quantum dot labeling solves these problems by providing safe and long life labels which are extremely sensitive and DNA-attachable (page 2016, first full paragraph). Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the radioactive labels of Söderlund et al with the quantum dot labels of Weiss et al based on the teaching of Chan et al for the obvious benefits of safety, label life, sensitivity and biocompatibility (Chan et al, page 2016, first full paragraph).

Regarding Claim 5, Söderlund et al teach their similar method wherein the primers comprises a biotinylated primer thereby producing a biotinylated DNA (Column 9, line 55-Column 10, line 8).

Regarding Claim 6, Söderlund et al teach their similar method comprising binding the transcribed target to a substrate (Column 10, lines 32-51).

Regarding Claim 7, Söderlund et al teach their similar method wherein the substrate comprises a streptavidin coated surface (Column 10, lines 32-51).

Regarding Claim 8, Söderlund et al teach their similar method further comprising removing unbound portions of target sequence i.e. washing (Column 10, lines 32-51).

Regarding Claim 9, Weiss et al teach the method comprising probing the bound target using a sequence-tagged hybridization probe (Column 15, lines 45-60).

Regarding Claim 10, Söderlund et al teach their similar method wherein the target comprises DNA having at least one point mutation (i.e. apolipoprotein E) and the probing comprises binding the probe to the at least one point mutation (Column 1, line 66-Column 2, line 7 and Column 10, lines 54-67).

Regarding Claim 11, Söderlund et al teach their similar method wherein the target comprises wild type DNA and probing comprises binding the probe to the wild type DNA i.e. wild type and mutant targets are detected (Column 11, lines 25-38).

Regarding Claim 12, Weiss et al teach the method further comprising removing non-specifically bound probes (Claim 115).

Regarding Claim 13, Weiss et al teach the method wherein the quantum dot has an attached oligonucleotide tag and labeling comprises binding each tag with a complementary sequence of each sequence-tagged hybridization probe (Column 15, lines 45-64).

Regarding Claim 14, Weiss et al teach the method further comprising removing unbound quantum dots (Claim 115).

Regarding Claim 15, Barbera-Guillem et al teach the method wherein the resolution is capable of detecting an optical characteristic of a single quantum dot (Column 18, lines 4-54).

Regarding Claim 18, Söderlund et al teach a method of detecting the presence of a single copy of a target nucleic acid in a sample comprising: transcribing a target nucleic acid

using a primer that is complementary to a portion of said target and that comprises an immobilizable label to form an immobilizable target sequence; immobilizing said immobilizable target on a solid support to form an immobilized target sequence; probing said immobilized target sequence using a sequence-tagged hybridization probe which is complementary to a portion of said target sequence; labeling said immobilized sequence; and detecting the labeled immobilized target sequence to thereby detect the presence of said target (Example 1, Column 9, line 50-Column 11, line 52) wherein the detected label is a radioactive label (Column 11, lines 17-24) but they do not teach a quantum dot conjugate wherein the conjugate comprises a quantum dot and nucleic acid sequence complementary to a portion of a hybridization probe. However, Weiss et al teach a similar method wherein the detection of the target is via quantum dot conjugates. Specifically, Weiss et al teach transcribing a target sequence, probing using a sequence-tagged hybridization probe complementary to a portion of the target sequence; labeling the target sequence with a quantum dot conjugate comprising a quantum dot and a nucleic acid sequence complementary to a portion of the probe; and detecting fluorescence emitted by the quantum dot to indicate the presence of the target sequence (Column 15, line 22-Column 16, line 35) wherein the quantum dot complexes are stable under various environmental conditions and permit simultaneous or sequential detection of a large number of targets (Column 29, lines 42-57). it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the radioactive label and detection of Söderlund et al with the quantum dot labeling and detecting as taught by Weiss et al because it was well known in the art that radioactive labels are hazardous and short lived as taught by Chan et al (first paragraph). Chan et al also teach that quantum dot labeling solves these problems by providing safe and long life labels which are extremely sensitive and DNA-attachable (page 2016, first full paragraph). Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the radioactive labels of Söderlund et al with the quantum dot labels of Weiss et al based on the

teaching of Chan et al for the obvious benefits of safety, label life, sensitivity and biocompatibility (Chan et al, page 2016, first full paragraph).

7. Claim 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss et al (U.S. Patent No. 6,207,392, filed 1 March 1999) and Babera-Guillem et al (U.S. Patent No. 6,221,602, filed 9 November 1999) as applied to Claim 1 above and further in view of Söderlund et al (U.S. Patent No. 6,013,431, filed 2 December 1993) in view of Chan et al (Science, 25 September 1998, 281: 2016-2018) as applied to Claim 6 above and further in view of Bawandi et al (U.S. Patent No. 6,306,610 B1, filed 17 September 1999).

Regarding Claim 16, Weiss et al teach a method of detecting the presence of at least one target nucleic acid sequence (i.e. detectable substance) in a sample comprising: labeling at least one target nucleic acid sequence with at least one quantum dot; and detecting the labeled target nucleic acid by detecting fluorescence emitted by the quantum dot wherein detection of fluorescence in the sample indicates the presence of at least one target nucleic acid sequence, wherein the labeling is via bonding of the nucleic acid affinity molecule to its complementary sequence (Column 4, lines 27-47 and Claim 114) and further comprising transcribing the target nucleic acid sequence i.e. PCR (Column 25,line 62-Column 26, line 48) wherein the quantum dot has an attached oligonucleotide tag and labeling comprises binding each tag with a complementary sequence of each sequence-tagged hybridization probe i.e. binding the oligonucleotide tag to a sequence to which the probe binds by complementation (Column 15, lines 45-64) but they do not specifically teach the transcribing provides a polymorphic region of DNA. However, transcribing a target sequence via PCR to produce polymorphic regions of DNA was well known and routinely practiced in the art at the time the claimed invention was made as taught by Söderlund et al. who teach a similar method of target detection comprising:

labeling at least one target nucleic acid sequence; and detecting the labeled target nucleic acid and they specifically teach transcribing the target using a primer which anneals to a conserved region of DNA to transcribe a polymorphic region of DNA (Example 1, Column 9, line 50-Column 11, line 52) wherein the primers comprises a biotinylated primer thereby producing a biotinylated DNA (Column 9, line 55-Column 10, line 8) and binding the transcribed target to a substrate (Column 10, lines 32-51).

Additionally, Söderlund et al teach that because numerous inherited diseases are caused by polymorphisms, methods for detecting polymorphic regions is are clinically important (Column 1, lines 35-65). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the transcription of a polymorphic target region of Söderlund et al to the transcription of Weiss et al based on the clinical importance of polymorphisms as taught by Söderlund et al (Column 1, lines 35-65). Therefore, one skilled in the art would have been motivated to transcribe and detect polymorphic regions of DNA for the obvious benefits of diagnosing clinically important DNA sequences.

Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the radioactive label and detection of Söderlund et al with the quantum dot labeling and detecting as taught by Weiss et al because it was well known in the art that radioactive labels are hazardous and short lived as taught by Chan et al (first paragraph). Chan et al also teach that quantum dot labeling solves these problems by providing safe and long life labels which are extremely sensitive and DNA-attachable (page 2016, first full paragraph). Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the radioactive labels of Söderlund et al with the quantum dot labels of Weiss et al based on the teaching of Chan et al for the obvious benefits of safety, label life, sensitivity and biocompatibility (Chan et al, page 2016, first full paragraph).

Weiss et al and Söderlund et al do not teach detecting comprises scanning the substrate with resolution capable of detecting fluorescence emitted by a single quantum dot (Claim 15) and they do not teach quantitating the target by counting the number of quantum does within an area (Claim 16). However, Chan et al and Bawandi et al teach that single quantum dot complexes are detectable and countable (Chan, page 2018, middle column, last paragraph and Bawandi, Column 28, lines 11-24). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the single quantum dot detection and counting of Chan et al and Bawandi et al to the quantum dot detection of Weiss et al to thereby detect and count a single quantum dots for the obvious benefits of analyzing real-time *in situ* events as taught by Chan et al (page 2018, middle column, last paragraph).

8. Claims 1-19 and 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cubicciotti et al (U.S. Patent No. 6,287,765, filed 20 May 1998) in view of Barbera-Guillem et al (U.S. Patent No. 6,221,602, filed 9 November 1999).

Regarding Claims 1-19 and 23-27, Cubicciotti et al teach a method of counting a single copy molecule of a target species immobilized on a substrate, said method comprising: detecting a single copy molecule of said target species by detecting an optical characteristic of label (Column 57, line 65-Column 59-11) attached to said single copy molecule, wherein said single copy molecule
is bound to an a first affinity moiety for said target species immobilized on said substrate and (Column 108, line 55-Column 109, line 16) wherein the labels are selected from colloids,

nanoparticles and fluorophores (Column 58, lines 13-15) wherein the labels are attached to said target species prior to binding said target species to said affinity moiety or after binding (Column 116, line 12-Column 117, line 13) and resolving said optical characteristic of labels attached to said single molecule to thereby count said single molecule (Column 206, lines 3-64).

Cubicciotti et al teach the method wherein the labels are resolved to count the molecules (Column 206, lines 3-64) and they teach the labels are selected from those known in the art e.g. from colloids, nanoparticles and fluorophores (Column 58, lines 13-15) but they do not specifically teach the labels are quantum dots. However, Barbera-Guillem et al teach the similar method wherein the preferred labels for resolution of and counting of molecules are quantum dots (Column 18, lines 4-54). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the resolving of Barbera-Guillem et al to the method of Cubicciotti et al to thereby resolve individual quantum dots for the expected benefit of sequencing the molecule based on the resolution as taught by Barbera-Guillem et al (Column 18, lines 4-54).

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 10 of copending Application No. 09/784,866. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to detecting a single copy target nucleic acid by detecting an optical characteristic of a first and second quantum dot and differ only in the '866 method is drawn to "counting" and comprising a detecting method step wherein the target is immobilized while the instant method is drawn to "detecting" the target nucleic acid and comprises a similar detecting step. However, instant claims 6-16 and are drawn to the immobilized target. Additionally, the '866 counting requires the instantly claimed detecting as evidenced by the method steps of the '866 claim. As such, both sets of claims are drawn to similar methods and differ only in the arrangement of the limitations within the claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response

11. Applicant's intent to file a terminal disclaimer upon indication of allowable subject matter is acknowledged.

Specification

12. The amendments to the specification, pages 55, 56, 57 and 58 are not in compliance with C.F.R. 37 § 1.121 (b)(1)(iii) which requires a marked up copy of the paragraphs be submitted.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741 until 13 January 2004. The examiner can normally be reached on 6:00 TO 3:30 Monday through Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-0507.

BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
January 16, 2004